November 25, 2008

Dear Dietary Guidelines Advisory Committee,

The scientific report from the 2005 Dietary Guidelines Advisory Committee was forward-looking in its recommendations regarding omega-3 fatty acids (n-3 FA) and the individual function and benefit of long chain n-3 FA (n-3 LCPUFA). Since 2005 the evidence demonstrating the benefit of n-3 LCPUFA and docosahexaenoic acid (DHA 22:6 n-3), in particular, has grown.

Since your Committee will utilize systematic reviews as the primary method for decision- making, we have assembled a systematic review of the n-3 LCPUFA literature since 2005 to determine the relationship of n-3 LCPUFA status and DHA status specifically to cardiovascular, neurocognitive, and developmental outcomes. Attached is a summary of this review. The entire review will be submitted directly to your attention and made available via your committee's evidence coordinator.

In short, the conclusions of our review show much progress towards resolving lingering questions from the 2005 Report. For example, the Committee noted that, "there is some evidence that consuming more than two servings of fish per week may confer further cardioprotective effects", evidence published since 2005 provides additional support for this observation. Specifically we would like the committee to note that:

- Data from current cardiovascular disease studies, representing 130,000 subjects collectively, provide strong evidence in support of dietary n-3 LCPUFA for the primary prevention of cardiovascular disease.
- Additional data from randomized controlled trials (RCTs) further suggest that n-3 LCPUFA supplementation ≥ 500 mg/d may significantly reduce blood pressure and heart rate, two surrogate markers for heart disease, among the general population.
- Recognizing that intakes greater than 500 mg/d may be difficult to achieve in the US based solely on fish consumption recommendations should be expanded to include alternative n-3 LCPUFA food sources and dietary supplements. In fact, the Health Council of the Netherlands, the Superior Health Council of Belgium, and the Heart Foundation of Australia have all endorsed n-3 LCPUFA fortified foods and capsules as alternative sources for people who do not readily consume fish.

In addition to cardiovascular health benefits, the evidence in support of DHA omega-3 for neurocognitive health and development continues to grow. The 2005 Report recognized an increased need for various nutrients in multiple population subgroups but failed to recognize the importance of dietary DHA among pregnant and nursing women, women of childbearing age, young children and the elderly. Evidence published since 2005 provides:

- Overwhelming support from observational studies indicating that n-3 LCPUFA from fish and DHA, in particular, provide cognitive benefit for adults over 50.

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- Results of up to 8 RCTs, suggesting a modest increase of up to 2.5 days in gestational duration in response to n-3 LCPUFA supplementation during pregnancy.
- Results of 5 recent RCTs and 1 observational study indicating that maternal DHA and/or n-3 LCPUFA intake, between 200-300 mg/d, during pregnancy or nursing positively influences neural development of infants and young children particularly with regard to vision-related outcomes.
- Support for expert group recommendations to include at least 200 mg DHA in the maternal diet during pregnancy and nursing and the need to educate US women concerning the potential benefits of DHA supplementation during pregnancy from safe sources of n-3 LCPUFA such as low methylmercury fish and dietary supplements from marine algal oil.

We look forward to hearing your discussions regarding n-3 LCPUFA and your methods for ensuring their inclusion in the US diet.

Respectfully submitted,

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Attachments (2)

1) Research Update on Long-Chain Omega-3 Fatty Acids since the 2005 Dietary Guidelines Advisory Committee Report
2) Research Update on Long-Chain Omega-3 Fatty Acids since the 2005 Dietary Guidelines Advisory Committee Report - References

Research Update on Long-Chain Omega-3 Fatty Acids since the 2005 Dietary Guidelines Advisory Committee Report

Summary of an Evidence-based Review

October 2008

Research Update on Long-Chain Omega-3 Fatty Acids Since the 2005 Dietary Guidelines Advisory Committee Report

Summary of an Evidence-based Review

Executive Summary

- An evidence-based analysis of the n-3 long-chain polyunsaturated fatty acid (LCPUFA) literature was conducted from late 2004 to the present in an effort to balance the information regarding docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) provided by the 2005 Dietary Guidelines (DG) and expand recognition of the health benefits of these important nutrients in the 2010 DG.

- Data from current cardiovascular disease studies, representing 130,000 subjects collectively, provide strong evidence in support of dietary n-3 LCPUFA for the primary prevention of cardiovascular disease.

- Additional data from randomized controlled trials (RCTs) further suggest that n-3 LCPUFA supplementation ≥ 500 mg/d may significantly reduce blood pressure and heart rate, two surrogate markers for heart disease, among the general population.

- Overwhelming support from current observational studies indicate that n-3 LCPUFA from fish, and DHA in particular, provide cognitive benefit for adults over 50.

- The results of up to 8 RCTs, as reported by two recent meta-analyses, suggest a modest increase of up to 2.5 days in gestational duration in response to DHA+EPA supplementation during pregnancy.

- The results of 3 recent RCTs and 1 observational study further indicate that maternal DHA and/or n-3 LCPUFA intake, between 200-300 mg/d, positively influences neural development of infants and young children particularly with regard to vision-related outcomes. Two RCTs of maternal DHA supplementation during nursing showed benefits for infant neural development. Finally, the majority of current RCT data indicate a benefit of direct post-natal supplementation of LCPUFA via DHA+ARA enriched infant formula to neurocognitive development in infants. This benefit also appears to continue to be measureable well beyond the period of supplementation and into childhood.

These data suggest that higher n-3 LCPUFA intake recommendations should be considered for the 2010 Dietary Guidelines and should reflect not only cardiovascular benefits but maternal and infant health as well as brain health for adults over 50. Vulnerable subgroups such as adults over 50 and pregnant/nursing women should be provided specific guidance regarding the importance of n-3 LCPUFA for good health. Recognizing that intakes greater than 500 mg/d may be difficult to achieve in the US, based solely on fish consumption, and that methyl-mercury from fish may be deleterious to pregnant/lactating women and young children, recommendations should be aligned with those of international government and expert groups and include n-3 LCPUFA fortified foods and dietary supplements as viable sources.

Introduction

The 2005 Dietary Guidelines Advisory Committee (DGAC) recognized the importance of dietary long-chain omega-3 fatty acids (n-3 LCPUFA) for cardioprotection among adults. The Committee noted that "a reduced risk of both sudden death and CHD death in adults is associated with the consumption of two servings (approximately eight ounces) per week of fish high in the n-3 fatty acids called eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)."[1] Unfortunately, the Committee's conclusions on this topic were significantly diminished in the final, published guidelines limiting recommendations for increased n-3 LCPUFA consumption to those "people who have already experienced a cardiac event." It further appears that n-3 LCPUFA intake may be protective throughout the lifecycle with regard to cognitive function among the ageing. While the 2005 The Committee recognized certain nutrient needs of adults over 50 there was no recognition of the growing body of evidence suggesting that dietary n-3 LCPUFA, and DHA in particular, may protect against age-related cognitive decline.

The Committee also recognized the vulnerable subpopulations of pregnant and nursing women and young children with regard to methyl-mercury contamination of fish, suggesting that intake of fish be limited in order to avoid or reduce exposure to environmental contaminants. The Committee did not, however, recognize any of the health benefits associated with n-3 LCPUFA among these subpopulations which include increased duration of gestation and support of fetal/infant neural development. In effect, the Committee provided women with a motive to exclude the richest source of DHA omega-3 when pregnant women may, indeed, need it the most.

Therefore, in an effort to provide a more balanced representation of the information regarding n-3 LCPUFA provided by the 2005 Dietary Guidelines and expand recognition of the health benefits of these important nutrients, an evidence-based analysis of the n-3 LCPUFA literature was conducted from late 2004 to the present. The following document highlights key findings of this evidence-based analysis which included examining the relationship between n-3 LCPUFA and 1. cardiovascular disease, 2. select cardiovascular disease risk factors, 3. cognitive function with age, 4. maternal health, and 5. infant neural development.

Methods

Methodologic details of the evidence-based process used, including specific search terms and inclusion exclusion criteria for each topic, are available upon request and will be supplied directly to the 2010 DGAC as part of a full evidence report. Briefly, potentially relevant studies were identified using a broad search of the clinical literature, involving both electronic and manual techniques. The search was conducted by the Professional Literature Search Service of the Health Sciences Library, University of Colorado Denver Anschultz Medical Campus. The databases searched included: Ovid Medline (1950-present, Indexed Citations); Ovid Medline (Old Medline and Other non-indexed citations); and EMBASE.

Two levels of study screening were employed. A level 1 screening was performed on abstracts obtained as the result of the search. At this level, any study with detectable, definite exclusion criteria was rejected. For the remaining studies, full papers were obtained and a level 2 screening was performed to assure all of the inclusion criteria were met. Generally, studies were excluded if they were: published in a language other than English; an abstract, letter, comment or review article without statistical treatment; included in-patient or high-risk populations; or reported only fish intake without estimation/determination of DHA+EPA intake.

[1] www.health.gov/dietaryguidelines/dga2005/report/PDF/A_ExecSummary.pdf, Pg. 5

Cardiovascular Health

Cardiovascular Mortality

The conclusions reached by the 2005 DGAC indicate that fish and n-3 fatty acids are associated with reduced risk of sudden death and coronary heart disease in healthy adults. The committee suggested that the weekly consumption of two servings of fatty fish, totaling about 500 mg n-3 LCPUFA/d, is needed to confer cardiovascular benefits. The Committee questioned if alternative sources such as supplements would provide similar benefits and also questioned if consuming more than two servings of fish per week might confer further cardioprotective effects. In an effort to support the ongoing efforts of the DGAC and bolster the case for general population fish and n-3 fatty acid recommendations the published literature was searched for primary preventions studies. Special attention was paid to unresolved issues from the 2005 assessment including the usefulness of supplements and the benefit of increased consumption greater than two servings of fish per week.

A total of 344 citations were screened at Level 1. Two systematic reviews/meta-analyses and 3 prospective cohort studies met all inclusion criteria. Additionally, 6 government recommendations/expert group opinions were identified (see reference list).

One systematic review (Wang et al., 2006) analyzed cardiovascular disease outcomes among one RCT, 25 prospective cohort studies and 7 case-control studies published between 1966 and July 2005 in populations with no history of heart disease. Most of the large cohort studies reviewed, totaling more than 340,000 participants, reported significant reductions in cardiovascular disease outcomes including cardiac death, sudden death, MI, and stroke after multivariate adjustment. The authors concluded that, "overall, the data from primary-prevention studies support the hypothesis that consumption of very-long-chain n-3 FAs from fish and fish-oil supplements reduces all-cause mortality, cardiac and sudden death, and stroke." In contrast, a meta-analysis by Hooper et al. (2006) failed to find a clear effect of n-3 LCPUFA on combined cardiovascular effects. Importantly, however, compared to the analysis conducted by Wang and co-workers the analysis by Hooper was quite heterogeneous and did not exclude studies due to poor methodologic quality. Additionally, while published in 2006, Hooper and co-workers only reviewed studies published by early 2002. The analysis of Wang et al. included at least 2 additional, positive cohort studies collectively representing over 6000 additional subjects, these differences may help explain the discrepancy between the two publications.

Among the prospective cohort studies, Iso et al. (2006) reported a clear relationship between increased intake of n-3 LCPUFA and reduced risk of coronary heart disease among 41758 healthy Japanese men and women from the Japan Public Health Center-based Study Cohort I (JPHC) after 10 years of follow-up. Moderate n-3 LCPUFA intake (600 mg/d) but not low intake (300 mg/d) was associated with a significant reduction in coronary heart disease outcomes. While all quintiles of n-3 LCPUFA intake, beginning with the second, reduced heart disease risk the highest quintile (2.1 g/d) resulted in the greatest reduction indicating that further benefit for reduced heart disease risk may be achieved at intake levels > 500 mg n-3 LCPUFA per day. The observation that reduced CHD risk in this study was related primarily to non-fatal coronary events expands the prior knowledge base which suggested the benefits of n-3 LCPUFA may be limited to reductions in sudden cardiac death. Mozaffarian et al. (2005) reported incidence of CHD among 45,722 members of the Health Professionals Follow-up Study cohort, men aged 40-75 years, over a 14 year period. High EPA+DHA intake, defined as $\geq$ 250 mg/d, was associated with a 35% reduced risk of sudden death (HR=0.65; CI – 0.47-0.88). Interestingly, varying ratios of intake for n-6 and n-3 PUFA were not significantly associated with CHD risk. Notably, dietary ALA was only associated with CHD risk among men with very low (< 100 mg/d) EPA+DHA intake. Collectively, these data indicate that n-3 LCPUFA may reduce the risk of sudden cardiac death regardless of n-6 fatty acid intake and that, as noted by the authors, the "relative intakes of n-3 and n-6 fatty acid may be less important than simply increasing the intake of n-3 PUFAs". Further support for the need to achieve an intake higher than the current suggested 500 mg/d comes from the study of Folsom and Demissie (2004). The authors found no association between fish or n-3 LCPUFA intake among postmenopausal participants in The Iowa Women's Health Study cohort (n=41,836) who were free of heart disease at baseline. Importantly, however, the highest quintile of intake (470 mg/d) was below that currently recommended for the prevention of heart disease. Finally, one prospective cohort reported an inconsistent association between n-3 LCPUFA intake and reduced heart disease risk among 5220 Finnish men and women (Jarvinen et al. 2006). Jarvinen and co-workers reported cardiovascular mortality outcomes after 21 years of follow-up noting a significant association between increased fish consumption, but not n-3 LCPUFA, and cardiovascular related mortality in women but not in men.

Collectively, these data indicate that evidence in support of fish and n-3 LCPUFA for the primary prevention of cardiovascular disease is growing. Evidence further suggests that 500 mg/d of n-3 LCPUFA may be the minimum suggested intake to result in this benefit and that higher intake recommendations should be considered. Recognizing that intakes greater than 500 mg/d may be difficult to achieve in the US based solely on fish consumption recommendations should be expanded to include alternative n-3 LCPUFA food sources and dietary supplements. In fact, the Health Council of the Netherlands, the Superior Health Council of Belgium, and the Heart Foundation of Australia have all endorsed n-3 LCPUFA fortified foods and capsules as alternative sources for people who do not readily consume fish.

Heart Rate and Blood Pressure

A total of 253 citations were screened at Level 1. One meta-analysis, one prospective cohort and 2 randomized controlled trials with heart rate as an outcome met all inclusion criteria. One meta-analysis, 2 prospective cohorts, and 3 randomized controlled trials, published since 2004 met all of the inclusion criteria and included blood pressure as an outcome.

Fish oil supplementation was included in a meta-analysis of randomized controlled trials investigating various individual lifestyle interventions associated with blood pressure reduction (Dickinson et al. 2006). In this meta-analysis, fish oil supplementation significantly reduced systolic blood pressure -2.3 mmHg and diastolic blood pressure -2.1 mm Hg. These results indicate that fish oil supplementation of about 4.5 g/d has modest but meaningful effects on blood pressure in mild to moderately hypertensive individuals.

Two randomized controlled trials, not included in the above meta-analysis, investigated lower levels of DHA+EPA supplementation with conflicting results. A study by Hill and co-workers (2007) reported the effects of 1.9 g/d of EPA+DHA during a 12-week study period among 75 subjects randomized to four different interventions. Interventions included supplemental fish oil or placebo combined with increased or no change in exercise habits resulting in about 18 subjects per group. No effect on blood pressure was noted despite this relatively high dose of EPA+DHA. In contrast, Theobald et al. (2007) studied 39 healthy, normotensive, male (bp 126/81) and female (bp 117/77) subjects ages 45-65 randomized in a cross-over design to either a DHA-rich supplement (700 mg/d) or refined olive oil placebo. A consistent, significant ($P<0.01$) reduction of -3.3 mm Hg in diastolic blood pressure was reported after the DHA supplement intervention.

The epidemiologic cross-sectional study, The International Study of Macro- and Micro-nutrients and Blood Pressure (INTERMAP; Ueshima et al., 2007) reported the influence of food based n-3 LCPUFA and blood pressure among 4680 men and women aged 40-59 from Japan, China, the US, and the UK. Long-chain n-3 fatty acids (790 mg/d) were inversely related to blood pressure with diastolic reductions ranging between -0.28 to -0.54 mmHg. These data are consistent with the RCT findings of Theobald et al. (2007) and support the role of at least 790 mg/d of long-chain n-3 fatty acid intake for a small decrease in diastolic blood pressure within the general population. Mozaffarian et al. (2006) also studied the association between fish and n-3 LCPUFA consumption and cardiovascular risk factors including blood pressure among participants (n=5073 men and women) in the US-based Cardiovascular Health Study. Intake of ≥ 3 fatty fish meals (tuna/other fish) per week or an estimated minimum of 608 mg EPA+DHA/d was associated with significantly lower (P<.01) blood pressure among normotensive older adults.

Collectively, the results of these studies suggest that lower doses (< 1 g/d) of n-3 LCPUFA may reduce blood pressure among normotensive subjects free of significant cardiovascular risk/disease but that higher doses may be required to lower blood pressure among hypertensive individuals or those with cardiovascular disease or multiple cardiovascular risk factors.

Mozaffarian et al. (2005) conducted a meta-analysis of RCTs to determine the effect of fish oil supplementation on heart rate. At total of 30 trials met all inclusion/exclusion criteria contributing 38 intervention groups and 1678 individuals, average age 54 years, treated with fish oil supplements or placebo for 27,615 person-weeks. Overall fish oil supplements decreased HR by 1.6 beats per minute (bpm; CI 0.6-2.5, P+0.002) compared to placebo. This would be consistent with an estimated 5% lower risk of sudden death. Further support for the potential benefits of low dose EPA+DHA supplementation (< 1 g/d) for heart rate reduction comes from a small RCT conducted by Shah and coworkers (2007). These investigators supplemented 26 healthy, normotensive individuals with either 500 mg/d EPA+DHA from fish oil versus a corn oil placebo for 14 days. Resting heart rate was significantly (P=.05) reduced by 5.9 bpm in response to fish oil supplementation at the end of the intervention compared to placebo from baseline levels of 67.5 bpm. An RCT by Geelen et al. (2005) reported a 2.1 bpm in response to fish oil supplementation (1.5 g EPA+DHA/day) vs. placebo (CI - -3.9, -0.3) after 14 days among subjects with an increased incidence of premature ventricular contractions (PVCs) and a resting heart rate of 75 bpm at baseline. Finally, a prospective cohort study by Mozaffarian and coworkers (2006) investigated the association between fatty fish, fried fish, or long-chain n-3 fatty acids and heart rate among participants in the US-based Cardiovascular Health Study. Intake of ≥ 3 tuna/other fatty fish meals per week or an estimated minimum of 608 mg EPA+DHA/d was associated with a significant (P<.01) decrease in resting heart rate among individuals averaging 69 bpm at baseline.

Based largely on the results of the meta-analysis and prospective study by Mozaffarian (2005 and 2006 respectively), it would appear than EPA+DHA supplementation >500 mg but < 1 g/d or at least 3 fish meals per week is associated with a decrease in resting heart rate of 1.6-3 bpm.

Adult Cognition

DHA omega-3 is an integral component of all mammalian membranes. It is the major structural and functional n-3 LCPUFA in the brain and retina. The presence of DHA at adequate levels in neural tissue is essential for optimal development of visual, cognitive, and vascular function.[2,3] Of particular interest in cognitive health during aging is inclusion of DHA in the diet. As a major component of the brain, DHA is

[2] Lauritzen, L. et al. (2001) Prog Lipid Res; 40:1-94.

[3] Salem, N. et al. (2001) Lipids 36:945-959.

involved in modulation of signal transduction molecules and in gene transcription. It is also the precursor for the family of compounds known as resolvins. These compounds are released in the brain in response to ischemic injury and are believed to be anti-inflammatory. [4] Early observational studies have shown that fish consumption is inversely correlated with cognitive impairments, including Alzheimer's disease. Specifically, consumption of more than one fish meal per week or greater than 60 mg DHA/d, has been associated with 60-70% less risk of incident Alzheimer's disease among US subjects.[5]

The current search identified 108 individual publications. The number of studies accepted at the level 1 screening totaled 25. After the level 2 screen, 14 studies (15 publications) were accepted for final review. These 15 publications represented 5 randomized controlled trials and 10 observational studies.

Observational studies included in this review are consistent in finding benefits of n-3 LCPUFA intake and/or blood biomarker status on cognitive function in the elderly. Five publications reported the use of food frequency questionnaires to determine intake of fish or intake of EPA and DHA. Upon stratification of the intake data, positive effects were seen on a variety of measures of cognitive function in healthy or cognitively impaired elderly subjects. Another five publications assessed DHA or DHA and EPA in blood parameters and found positive outcomes for varying cognitive parameters. One of the studies, by Schaefer et al. (2006) studied 899 men and women from the Framingham cohort with an average age of 76 years over a nine year period. None of the participants had dementia at the beginning of the study, but following up to an average of nine years later, there were a documented 99 cases of dementia, including 71 with Alzheimer's disease. Subjects with the highest blood levels of DHA had a 47% reduced risk of dementia, compared to the three-quarters of subjects with lower DHA levels, and a 39% lower Alzheimer's risk.

The majority of accepted RCTs found some form of cognitive improvement for the elderly as the result of n-3 LCPUFA supplementation. Freund-Levi et al. (2006) published the neurocognitive outcomes of a RCT (OmegAD) in which subjects with varying stages of Alzheimer's disease were given a fish oil supplement containing 1.7 g DHA/d for 6 months. Although the subjects with highly progressed disease showed no improvement, those with very mild cognitive dysfunction (MMSE >27) showed a significantly reduced rate of decline on the MMSE as compared to the placebo group. Chui et al. (2008) conducted a 24 week RCT which supplemented subjects with either Alzheimer's disease or cognitive impairments with 1.8 g/day of n-3 LCPUFA per day (720 mg DHA/day) or olive oil placebo. The treatment groups showed better improvement on the Clinician's Interview-Based Impression of Change Scale. Treated subjects with mild cognitive impairment showed better scores than placebo on the Alzheimer's Disease Assessment Scale while those diagnosed with the disease did not. One accepted RCT, Van de Rest et al. (2008), failed to find differences in scores of cognition in older subjects given fish oil to provide either 847mg or 176mg DHA/d for 26 weeks vs. placebo. All groups in this study showed learning effects over time, however, indicating the assessment tool used was not sensitive enough to discriminated differences in these subjects.

Overwhelming support from observational studies indicate that n-3 LCPUFA from fish, and DHA in particular, provide cognitive benefit for the elderly. Unfortunately RCT data in this area is limited.

[4] Salem, N. et al. (2001) Lipids 36:945-959.

[5] Morris, M. et al. (2003) Arch Neurol 60:940-6.

However, ongoing clinical trials with DHA from algal oil may provide RCT support for supplementation of n-3 LCPUFA for the prevention of age-related cognitive decline and Alzheimer's disease.[6,7] Until additional RCT data is available it seems prudent, based on strong observational data, to recognize healthy brain function over the age of 50 as one of the many potential benefits associated with increased consumption on n-3 LCPUFA-rich foods.

Maternal Health

A total of 51 citations were screened at Level 1. Three systematic reviews/meta-analyses, 2 RCTs, and 4 observational studies met all inclusion criteria. Additionally, 9 government recommendations/expert group opinions were identified (see attached reference list).

Two meta-analyses (Makrides et al. 2006, Szajewska et al., 2006) distinguished between RCTs of women with low-risk vs. hi-risk pregnancies while one meta-analysis (Lewin et al., 2005) combined gestational duration data without regard to risk status. Meta-analyses that looked exclusively at high-risk pregnancies were excluded from the current review as they would not be representative of the general pregnant population. Makrides and co-workers collectively analyzed data from 1621 women with low-risk pregnancies participating in 3 RCTs. The authors found a small but consistent increase (P=0.01) of 2.6 days (95% CI 1.03-4.07 days) in length of gestation associated with n-3 LCPUFA intake ranging between 133 mg – 3 g EPA+DHA per day from dietary supplements and enriched foods. The authors also reported a 47 g increase (95% CI 1-93 g) in birth weight and a 0.48 cm (95% CI 0.13-0.83 cm) increase in birth length among infants born to supplemented women. Similar to the findings of Makrides et al. (2006), Szajewska et al. (2006) reported a significant increase in gestation duration (P=0.01) associated with maternal EPA+DHA intake, however, the inclusion of some poorer quality studies resulted in an apparent decrease in the effect size to 1.57 days (95% CI:0.31,2.87 days). In contrast to the above meta-analyses of gestation duration (continuous variable expressed in days), Lewin and co-workers (2005) meta-analyzed the incidence of premature delivery (dichotomous variable) from eight RCTs of women with normal or high-risk pregnancies. Owing to the heterogeneity of include studies, particularly with regard to risk status, and the dichotomous nature of their endpoint the authors failed to find a benefit for n-3 LCPUFA and preterm birth reduction. Two RCTs not included in the above meta-analyses met all of the current inclusion criteria (Knudsen et al., 2006; Krauss-Etschmann et al., 2007). Unfortunately, neither of these studies was of sufficient methodologic or experimental design quality to yield useful information.

Two observational studies published since the 2005 DG explored the relationship between dietary DHA+EPA and gestation duration (Oken et al. 2004; Rogers et al., 2004) but found no benefit of maternal dietary n-3 LCPUFA intake on length of gestation. It is important to note that not only are these two observational studies in conflict with results from high quality meta-analyses of RCT data discussed above, they are also directly countered by results of two earlier observational studies. In a large study of Danish women (n=8729), enrolled at 16 weeks' gestation, Olsen and Secher (2002)[8] reported at 3.6 day increase in gestation duration between the highest (445 mg/d long-chain n-3) and the lowest (38 mg/day)

[6] http://clinicaltrials.gov/ct2/show/NCT00440050?term=Martek+Biosciences&rank=9

[7] http://clinicaltrials.gov/ct2/show/NCT00278135?term=Martek+Biosciences&rank=4

[8] Olsen SF and Secher NJ, 2002. BMJ 324:447.

quintiles of intake (P=0.001). The authors noted that the effect was strongest below an estimated daily intake of 150 mg/d long-chain n-3 or 15 g fish per day. Grandjean and co-workers (2001) observed 182 women during pregnancy reporting that a 1% increase in cord serum phospholipid DHA was associated with a 1.5 day increase in duration of gestation (P<.001; 95% CI 0.7-2.2).[9]

Collectively the results of up to 8 RCTs, as reported by two recent meta-analyses, suggest a modest increase of up to 2.5 days in gestational duration in response to DHA+EPA supplementation. Observational results are equivocal with regard to DHA+EPA intake and gestational duration. Full-term gestation is achieved at $\geq$ 37 weeks but $\leq$ 42 weeks gestation. Births prior to 37 weeks but greater than 34 weeks are considered late preterm and are associated with a higher incidence of morbidity and mortality when compared with term infants.[10] Late preterm infants comprise approximately 71% of all preterm births in the US and account for the majority of the increase in preterm birth rates over the past two decades. Therefore, interventions resulting in even modest prolongations of gestation may be important. These data, along with expert group recommendations, support the need to educate US women concerning the potential benefits of modest EPA+DHA supplementation during pregnancy from safe sources of n-3 LCPUFA such as low methyl-mercury fish and dietary supplements from marine algal oil.

Infant Neural Development

The most rapid and critical period of brain growth, development, and DHA accretion is during the brain growth spurt, from late gestation up to 4 years of age. During this time, brain mass increases approximately 3-fold and the DHA content increases from approximately 2 to 4.5 g.[11] [12] DHA is passed to the infant from the mother via the placenta during gestation and via breast milk following birth. Human milk always contains DHA, although the level can be affected greatly by maternal diet. Clinical studies demonstrate benefits to the infant from adequate DHA levels supplied from breast milk, infant formula, or from the maternal diet during pregnancy and nursing.

To date, more than 14 controlled clinical trials have been completed that compare formula feedings with and without added LCPUFA. The literature consists of reports of both positive and null findings, with an almost complete absence of negative or adverse effects. Differences in dose and duration of supplementation, subject selection, and the diversity and variability of primary outcomes contribute to the previous lack of agreement in the literature. Recent statistical summations of the literature, however, strongly support the efficacy of LCPUFA supplementation, particularly that of DHA in early visual development.[13] The information below outlines the benefits to infant neural development from either maternal prenatal supplementation during pregnancy, maternal post-natal supplementation during lactation, or direct post-natal supplementation of the infant via LCPUFA infant formula.

[9] Grandjean P, et al., 2001. Int J Epidemiol 30:1272-8.

[10] Institute of Medicine (2006). Preterm Birth: Causes , Consequences, and Prevention. www.iom.edu/Object.File/Master/35/975/pretermbirth.pdf

[11] Yuhas, R. et al. (2006) Lipids 41:851-858.

[12] Jensen, C. et al. (2005) Am J Clin Nutr 82(1):125-132.

[13] SanGiovanni, J. et al. (2005) Prog Retin Eye Res 2005; 24:87-138.

Since the 2005 Dietary Guidelines, 3 RCTs of maternal DHA supplementation during pregnancy and 2 RCTs of maternal DHA supplementation during nursing and the effects on infant neural development met all the inclusion criteria for the current review.

Specifically, studies by Dunstan and co-workers (2008), Innis and Friesen (2008) and Judge et al. (2007) all report significant improvements in visual outcomes following maternal n-3 LCPUFA supplementation during pregnancy. Dunstan and co-workers (2008) reported significantly improved hand-eye coordination among 2.5 year old children of women (n=98) supplemented with 3.3 g of n-3 LCPUFA from fish oil (2.2 g DHA, 1.1 g EPA) from the 20th week of gestation to delivery. Innis and Friesen (2008) supplemented 135 Canadian women with 400 mg DHA/d from algal oil beginning in the 16th week of gestation and found that at 2 months of age, infants in the placebo group were significantly more likely to have a lower visual acuity score than infants born to mothers supplemented with DHA. Finally, Judge et al. (2007) reported a significant, but transient, improvement in visual acuity among 4 month old but not 6 month old infants of mothers (n=30) supplemented with 214 mg/d of DHA from cereal bars produced with low-EPA fish oil beginning in the 20th week of gestation.

Two RCTS (Jensen et al., 2006; Lauritzen et al., 2005) studied the effects of maternal DHA supplementation during the first four months of lactation with mixed results. Lauritzen and co-workers supplemented Danish women with estimated background diet intakes of < 400 mg n-3 LCPUFA/d with 900 mg of DHA from 1.5 g of fish oil daily. Similar to Innis and Friesen, Lauritzen noted a sex difference for outcomes with a significant improvement of problem solving skills among girls but not boys at 9 months of age and a significant reduction in verbal skills among boys at 1 year of age but not at two years. Jensen and co-workers (2005) supplemented 227 US women during the first 4 months of lactation with 200 mg/d of DHA from algal oil. The authors reported a significant improvement in response to maternal DHA as children supplemented with DHA from enriched breast milk during the first four months of life scored significantly higher on the psychomotor subscale of the Bayley's Development test. Finally, Oken and co-workers studied the influence of maternal fish intake during pregnancy on measures of neural development at 3 years of age among 341 US mother/child pairs participating in Project Viva. Maternal fish intake more than twice a week or just over 300 mg DHA+EPA per day was associated with significant performance improvements on tests of language and visual motor skills. Additionally, the authors found that for each 100 mg of maternal daily DHA+EPA intake from fish, children had higher Peabody Picture Vocabulary scores that were 0.5 points higher (95% CI -0.5, 1.5) and Wide Range Assessment of Visual Motor Abilities scores that were 1.1 points higher.

Collectively, the results of 4 recent RCTs indicate that maternal DHA and/or DHA+EPA intake from fish positively influences neural development of infants and young children particularly with regard to vision-related outcomes. In the current studies, benefits were achieved with supplemental levels as low as 200-300 mg/day DHA per day. These results are consistent with expert group recommendations for women to achieve an n-3 LCPUFA intake that provides at least 200 mg daily during pregnancy and nursing.[14] Data from the above studies further support the use of low-methyl mercury fish, dietary supplements, or DHA fortified foods to achieve DHA intake recommendations during pregnancy and nursing.

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[14] (ISSFAL, 2008) International Society for the Study of Fatty Acids and Lipids (ISSFAL). PUFA Recommendations. www.issfal.org.uk/pufa-recommendations.html

The accepted studies regarding direct post-natal supplementation of infants via infant formula included 9 randomized controlled trials, 1 observational study, and 1 meta-analysis reporting a visual, neurocognitive, or anthropometric outcome.

Although a number of meta-analyses were published between January 2005 and August 2008 regarding this topic, all except for the study by Morale et al, include studies which used very low levels of DHA supplementation, DHA supplementation without concurrent ARA (current standard of care), or supplement period lasting less than three months, three of the prominent exclusion criteria used by this review. In the publication by Morale et al (2005), data from 243 infants who participated in four randomized controlled trials at the Southwestern Eye Institute in Dallas, Texas were combined. The intervention in each study was the use of DHA and ARA supplemented formula (0.36% and 0.72% total fatty acids, respectively). Results showed that infants receiving preformed DHA and ARA had better sweep visual acuity at 52 weeks. There was also an advantage of continuing the supply of LCPUFA throughout the first year.

Birch et al published two randomized clinical trials (2005, 2007) which demonstrated a visual and neurocognitive benefit for formula fed infants receiving DHA supplementation as compared to control. More importantly, these studies add to the literature which shows that the benefits of including DHA in early life extended well beyond the period of supplementation into childhood. The study included 103 term infants supplemented with either and infant formula containing 0.36% DHA and 0.72% ARA or formula with no DHA or ARA supplementation. VEP acuity in the supplemented group was significantly better than the unsupplemented group at 12 months of age. In the second Birch publication (2007), the authors conducted a follow-up of a cohort of infants who were fed either infant formula containing 0.36% DHA and 0.72% ARA during the first 17 weeks of life, 0.36% DHA only, or formula without supplementation. A group of breastfed infants was also followed as a standard for comparison. Only the infants who received DHA/ARA supplemented formula had visual acuity and Verbal IQ scores equal to that of breast-fed children at 4 years of age. In addition, only the infants who received DHA only had poorer Verbal IQ than the breast-fed infants. Both of these studies clearly demonstrate the benefits of early DHA and ARA supplementation on later development.

Trials by Clandinin et al in 2005 and by Henriksen in 2008 compared outcomes of DHA and ARA supplementation to control in studies of premature infants. In the study by Clandinin DHA and ARA supplemented groups scored higher on Bayley mental and psychomotor development scores at 118 weeks post menstrual age (approximately 18 months of chronological age) than controls. The randomized, double-blind placebo-controlled study by Henriksen et al had a unique design where 141 premature infants received fortified human milk, half of which also receive DHA and ARA supplementation from week one through hospital discharge. The DHA/ARA supplemented group showed better recognition memory and higher problem solving scores at 6 months of age as compared to control. These two trials demonstrate the benefit of early DHA/ARA feeding on neurocognitive outcomes in preterm infants.

Two RCTs failed to show benefit of DHA and ARA supplementation. Bouwstra et al (2005) compared DHA and ARA supplemented or control-fed infants at 18 months of age. The primary outcomes of the prospective, double blinded study included general movements, and neurodevelopment as measured by the Hempel and Bayley scales. At the 18 month follow up, the groups did not show difference in general movement, neurological optimality score, fluency score, or psychomotor and mental development scores that had been present at two months. Similarly, the follow up of a cohort by Singhal, et al showed that a comparison of DHA and ARA supplemented infants with a control group failed to show differences in measures of visual acuity at 4-6 years of age. Three additional RCTs recorded growth parameters of infants fed a supplemented formula compared to control. No significant difference was found in weight, length, or head circumference of infants receiving DHA- and ARA- supplemented formula compared to those receiving an unsupplemented control formula (Groh-Wargo et al. 2005; Hoffman et al. 2008; Siahanidou et al. 2007). The primary outcomes of these formulas did not include cognitive or visual assessment.

A multi-center, open label, observational study by Pastor et al (2006) gathered data from 1342 infants fed either DHA/ARA-supplemented or unsupplemented infant formula. The growth characteristics were similar for both groups. There was a higher incidence of bronchiolitis in the control group at 5, 7, and 9 months.

Most, but not all randomized controlled trials completed between January 2005 and August 2008 demonstrate a benefit of direct post-natal supplementation of LCPUFA, including DHA omega-3, to neurocognitive development in infants. This benefit also appears to continue to be measureable well beyond the period of supplementation and into childhood.

Conclusions

The results of the current evidence-based analysis provide support for DG recommendations to increase n-3 LCPUFA intake. Specifically, at least 3 servings of fish per week or approximately 750 mg of DHA+EPA may help reduce the risk of CHD, lower blood pressure and decrease heart rate among the general population. Older adults should be advised to increase the intake of fish and/or n-3 LCPUFA to support brain health with ageing. Women of childbearing age and pregnant/nursing women should be advised not only to avoid environmental contaminants from fish but seek alternative n-3 LCPUFA sources to support maternal health and infant neural development. Evidence further supports supplementation of diets for infants and young children with DHA from a variety of foods or via post-natal maternal DHA supplementation to promote visual development. The data reviewed herein supports the benefits not only of fish but of n-3 LCPUFA dietary supplements and fortified foods for good health.

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Full report to be submitted to the 2010 Dietary Guidelines Advisory Committee as part of official comment period

Research Update on Long-Chain Omega-3 Fatty Acids Since the 2005 Dietary Guidelines Advisory Committee Report

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